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CLINICAL RESEARCH
Pacing and resynchronization therapy

Heart failure in patients with sick sinus syndrome treated with single lead atrial or dual-chamber pacing: no association with pacing mode or right ventricular pacing site

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Aims

Previous studies indicate that ventricular pacing may precipitate heart failure (HF). We investigated occurrence of HF during long-term follow-up among patients with sick sinus syndrome (SSS) randomized to AAIR or DDDR pacing. Furthermore, we investigated effects of percentage of ventricular pacing (%VP) and pacing site in the ventricle.

Methods and results

We analysed data from 1415 patients randomized to AAIR ($n = 707$) or DDDR pacing ($n = 708$). Ventricular pacing leads were recorded as located in either an apical or a non-apical position. The %VP and HF hospitalizations were recorded during follow-up. Patients were classified with new HF, if in New York Heart Association (NYHA) functional class IV or if presence of ≥ 2 of: oedema; dyspnoea; NYHA functional class III. Mean follow-up was 5.4 ± 2.4 years. Heart failure hospitalizations did not differ between groups. In the AAIR group, 170 of the 707 (26%) patients developed HF vs. 169 of the 708 (26%) patients in the DDDR group, hazard rate ratio (HR) 1.00, 95% confidence interval (CI) 0.79–1.22, $P = 0.87$. In DDDR patients, 146 of the 512 patients (29%) with ventricular leads in an apical position developed HF vs. 28 of the 161 patients (17%) with the leads in a non-apical position, HR 0.67, CI 0.45–1.00, $P = 0.05$. After adjustments this difference was non-significant. The incidence of HF was not associated with %VP ($P = 0.57$).

Conclusion

In patients with SSS, HF was not associated with pacing mode, %VP, or ventricular lead localization. This suggests that DDDR pacing is safe in patients with SSS without precipitating HF.

Keywords

Sick sinus syndrome • Sinoatrial node • Pacemakers • Heart failure • Pacing

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[†] Participants in The Danish Multicenter Randomized Trial on Single Lead Atrial Pacing versus Dual Chamber Pacing in Sick Sinus Syndrome (DANPACE) are listed in the Appendix. Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2012. For permissions please email: journals.permissions@oup.com.

Introduction

Patients with sick sinus syndrome (SSS) and bradycardia can be treated by either a single-lead atrial pacemaker (AAIR) or a dual-chamber pacemaker (DDDR). Recently, The Danish Multicenter Randomized trial on single-lead atrial pacing vs. dual-chamber pacing in sick sinus syndrome (DANPACE) trial comparing AAIR and DDDR pacing in SSS found no difference in mortality between the two groups.¹

The AAIR pacing preserves a normal contraction pattern similar to the one seen during sinus rhythm, whereas DDDR pacing may lead to abnormal contraction patterns in the ventricles.²

In some patients, the abnormal contraction pattern seen during ventricular (DDDR) pacing may lead to left ventricular remodeling, decreased left ventricular function, and dilatation of the left atrium.^{3–5} Further, there is an association with increased incidence of atrial fibrillation and heart failure (HF).^{6–9}

Right ventricular apical pacing has been proposed to precipitate HF as opposed to septal (right ventricular septal, RVS) and outflow tract (right ventricular outflow tract, RVOT) pacing.^{2,10,11} These studies, however, have generally included only small numbers of patients, and large randomized trials are yet to prove that a non-apical pacing site is superior in a clinical context.

Therefore, we examined data from the DANPACE trial with the aim of determining the effect of DDDR pacing as compared with AAIR pacing with respect to the development of HF judged by hospital admissions for HF, symptoms, and medication. Furthermore, in patients randomized to DDDR pacing, we examined the effect of apical pacing compared with non-apical pacing with respect to the development of HF.

Methods

Study design

The DANPACE trial has been described previously.¹ In brief, the trial randomly assigned 1415 patients with SSS to AAIR or DDDR pacing.

The criteria for inclusion were: symptomatic bradycardia; documented sino-atrial block or sinus-arrest with pauses >2 s or sinus bradycardia <40 b.p.m. for >1 min while awake; PR interval ≤ 0.22 s if aged 18–70 years or PR interval ≤ 0.26 s if aged ≥ 70 years; and QRS width <0.12 s.

The main exclusion criteria were: atrio-ventricular block; bundle branch block; long-standing persistent atrial fibrillation (>12 months); atrial fibrillation with ventricular rate <40 b.p.m. for ≥ 1 min or pauses >3 s; a positive test for carotid sinus hypersensitivity.

Enrollment began in March 1999 and was terminated in June 2008. Patients were followed until September 2009.

The trial was conducted in accordance with the Helsinki Declaration and approved by the regional Ethics Committee and the Danish Data Protection Agency. All patients gave written informed consent before inclusion.

Implantation and programming of pacemakers

A bipolar lead was implanted in the right atrium, and in patients randomized to DDDR pacing an additional lead was implanted in the right ventricle. The position of the ventricular lead was noted in the

frontal fluoroscopy plane as being in either an apical or non-apical position.

The rate-adaptive function was activated in all pacemakers and programmed with a lower rate of 60 and an upper rate of 130 b.p.m. In patients with DDDR pacemakers, the paced atrio-ventricular interval (AVI) was programmed to 140–220 ms according to a pre-specified algorithm.¹ The maximum tracking rate was individualized and the mode switch function was activated.

Patient follow-up

Follow-up took place after 3 months and again every year after implantation up to 10 years. Mean follow-up was 5.4 ± 2.6 years. At each planned follow-up visit, a printout was made of the pacemaker memory data accumulated since the previous resetting of the memory. The percentage of ventricular pacing (%VP) at each follow-up was calculated using the number of paced and the number of sensed beats. Furthermore, information regarding HF: New York Heart Association (NYHA) functional class, presence of oedema, presence of dyspnoea, and medication was collected. The investigators were asked to only change the pacing mode from AAIR to DDDR pacing in cases of high-grade atrio-ventricular block or documented symptomatic atrio-ventricular block of Wenckebach type.

Definition of heart failure

The primary endpoint was hospitalization with HF as reported diagnosis. Furthermore, as a secondary endpoint, patients were classified with new HF if: (i) they presented in NYHA functional class IV or (ii) if two or more of the following indicators were present: presence of oedema, presence of dyspnea, and NYHA functional class III.

Statistical analysis

The time until HF hospitalization and the aforementioned HF indicator criteria were first met was analysed with Cox proportional hazard regressions. Only crude analysis is reported for HF hospitalizations due to the small number of events. Following the lines of the first reporting from the DANPACE trial, stratified analyses of each of a number of pre-specified confounders were performed (Figures 3 and 4). Furthermore, an analysis adjusting for main effects including all confounders is reported. Pacing modes were compared on an intention-to-treat basis and reported as hazard rate ratios (HR). Analysis of ventricular lead positions and %VP were done in patients who received DDDR pacemakers regardless of initial randomization and reported analogously to pacemaker-type comparisons.

The potentially non-linear relationship between development of HF and %VP⁸ that was indicated by the initial analysis was analysed by fitting fractional polynomials¹² in a Cox regression with %VP being a time-varying covariate.

Statistical tests were two-tailed, and $P < 0.05$ was considered significant. Stata version 11.2 (StataCorp. 2009. Stata: Release 11. Statistical Software. College Station, TX, USA: Stata Corp LP) was used.

Results

Population

A total of 1415 patients were included in the analysis. Of these, 708 patients were randomized to receive a ventricular lead in the DDDR group. Among patients randomized to AAIR pacing, 122 patients (17%) received a ventricular lead at the initial operation or sometime during follow-up. Baseline characteristics of

Table 1 Baseline characteristics of the patients

Characteristic	AAIR (n = 707)	DDDR (n = 708)	P value
Female gender, n (%)	472 (67)	441 (62)	0.08
Age, years (mean \pm SD)	73.5 \pm 11.2	72.4 \pm 11.4	0.054
Prior history of atrial fibrillation, n (%)	303 (43)	318 (45)	0.44
Hypertension, n (%)	241 (34.1)	239 (34)	0.90
Previous myocardial infarction, n (%)	94 (13)	90 (13)	0.74
Left ventricular ejection fraction reduced (<50%), n (%)	59 (11)	54 (10)	0.55
Left ventricular end-diastolic diameter in mm, mean \pm SD	47.7 \pm 7.3	47.8 \pm 7.3	0.45
Symptoms before pacemaker, n (%)			
Syncope	359 (51)	349 (49)	0.58
Dizzy spells	597 (84)	587 (83)	0.44
Heart failure	86 (12)	79 (11)	0.56
≥ 2 of the above three symptoms	317 (45)	291 (41)	0.16
Medication at randomization, n (%)			
Beta-blocker	159 (23)	132 (19)	0.08
Calcium-channel blocker	137 (19)	142 (20)	0.75
Digoxin	73 (10)	62 (9)	0.32
Angiotensin-converting enzyme inhibitors	160 (23)	170 (24)	0.53
Diuretics	304 (43.0)	263 (37)	0.03
NYHA class, n (%)			0.33
I	503 (71)	522 (73.9)	
II	172 (24)	158 (22.4)	
III	29 (4)	24 (3.4)	
IV	0	2 (0.3)	

SD, standard deviation; NYHA, New York Heart Association.

patients in the main trial as well as patients who developed HF after pacemaker implantation are presented in *Tables 1* and *2*.

The analysis is based on a total of 7496 follow-up visits in 1392 patients spanning over a period of 5.4 ± 2.6 years.

Heart failure

Pacing mode and heart failure

Hospitalization for HF occurred in 27 patients in the AAIR group vs. 28 patients in the DDDR group [HR 1.06; 95% confidence interval (CI) 0.62–1.79, $P = 0.84$] (*Figure 1*).

There was no difference in NYHA class at inclusion (*Table 1*) or at last follow-up, where the number of patients in class I/II/III/IV were 341/260/61/4 in the AAIR group vs. 364/231/67/4 in the DDDR group, $P = 0.43$. In the AAIR group, 170 patients (26%) developed new HF during follow-up vs. 169 patients (26%) in the DDDR group, HR 1.00; 95% CI 0.79–1.22, $P = 0.87$. Time-to-event curves for HF are displayed in *Figure 2*. Hazard ratios for the development of HF adjusting for different variables

are displayed in *Figure 3* (intention-to-treat analysis). The smallest P values for substrata effect of pacing mode were 0.05, for both substrata 'age ≤ 75 years' HR 0.72; 95% CI 0.53–1.00, and substrata 'age > 75 years' HR 1.34; 95% CI 1.00–1.80. All other variables were non-significant ($P > 0.31$). A fully adjusted hazard ratio showed no significant effect of pacing mode (AAIR vs. DDDR) on the development of HF, HR 1.09; 95% CI 0.88–1.35, $P = 0.44$. Both development of clinical HF and hospitalization for HF were strongly associated with the following baseline characteristics: older age, reduced left ventricular ejection fraction, previous myocardial infarction (MI), use of diuretics, and higher NYHA class (*Table 2*).

Pacing site and ventricular pacing

In patients randomized to DDDR pacing 28 of the 161 patients (17%) with leads in a non-apical position developed HF during follow-up as compared with 146 of the 512 patients (29%) with leads in an apical position, HR 0.67; 95% CI 0.45–1.00, $P = 0.05$. A per protocol analysis with hazard ratios for the development of HF, adjusted for different variables, is displayed in *Figure 4*. A fully adjusted hazard ratio showed no significant interaction between apical or non-apical pacing with respect to the development of HF, HR 0.76; 95% CI 0.50–1.14, $P = 0.18$.

The median percentage of ventricular pacing in the DDDR group was 85% (interquartile range 34–99%). *Figure 5* displays the hazard ratio for development of HF in relation to different levels of mean %VP.

No significant association was found between %VP and the development of HF, fractional polynomial vs. no relationship, $P = 0.57$.

Discussion

In the hitherto largest randomized setting, the present study investigated the impact of pacing mode on the development of HF in patients with SSS. The main findings of the study were that no significant difference was found between AAIR and DDDR pacing. Furthermore, in patients with a ventricular lead, an apical as compared with a non-apical position was not associated with development of HF, nor was %VP.

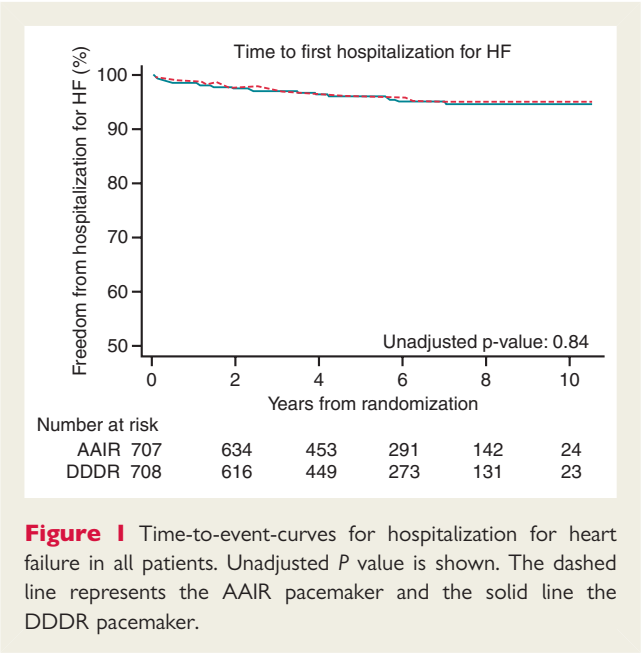
Heart failure and pacing mode

In recent years, increasing attention has focused on minimizing the amount of ventricular pacing in pacemaker recipients, especially in the case of SSS without impaired AV conduction.⁹ In small trials in patients with SSS, DDDR pacing was associated with more atrial fibrillation, increased left atrial diameter, and decreased left ventricular performance as assessed by M-mode and tissue Doppler echocardiography.^{3,13,14} However, the impact of DDDR pacing on the development of HF remains unclear in a broader clinical setting. With 1415 enrolled patients, the present study is the first to demonstrate that DDDR pacing has no statistically significant impact on the development of HF in SSS as compared with AAIR pacing. These results probably reflect that the modest effects on left ventricular function of right ventricular pacing—an absolute decrease in ejection fraction of $\sim 5\%$ ⁵—is tolerated and rarely causes clinical HF in patients who have a normal systolic

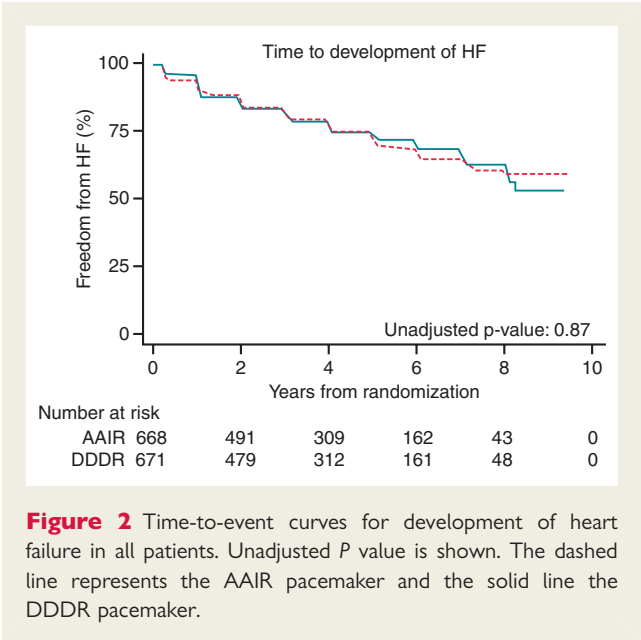
Table 2 Baseline characteristics of patients with and without heart failure

Characteristic	Hospitalization for HF		P value	Development of HF		P value
	Yes (n = 55)	No (n = 1360)		Yes (n = 373)	No (n = 1019)	
Female gender, n (%)	41 (75)	872 (64)	0.15	281(75)	615 (60)	<0.01
Age, years (mean ± SD)	77.0 ± 9.9	72.8 ± 11.3	<0.01	75.1 ± 10.2	72.1 ± 11.6	<0.01
Hypertension, n (%)	12 (22)	468 (34)	0.06	136 (36)	334 (33)	0.20
Previous myocardial infarction, n (%)	14 (25)	170(13)	0.012	61 (16)	116 (11)	0.018
Left ventricular ejection fraction reduced (<50%), n (%) ^a	16 (29)	97 (7)	<0.01	46 (12)	65 (6)	<0.01
Left ventricular end-diastolic diameter in mm, mean ± SD	47.3 ± 7.1	47.8 ± 10.5	0.69	47.4 ± 8.1	47.9 ± 6.9	0.29
Medication at randomization, n (%)						
Beta-blocker	11 (20)	280 (21)	1.00	85 (23)	202 (20)	0.23
Calcium-channel blocker	11 (20)	268 (20)	1.00	77 (21)	196 (19)	0.60
Digoxin	10 (18)	125 (9)	0.04	45 (12)	84 (8)	0.04
Angiotensin-converting enzyme inhibitors	21 (38)	309 (23)	0.01	94 (25)	229 (22)	0.32
Diuretics	34 (62)	533 (39)	<0.01	208 (56)	347 (34)	<0.01
NYHA class, n (%)			0.007			<0.01
I	29(53)	996 (73)		221 (59)	792 (78)	
II	22 (40)	308 (23)		123 (33)	200 (20)	
III	4 (7)	49 (4)		28 (8)	23 (2)	
IV	0	2 (<1)		1 (<1)	0 (0)	

HF, heart failure; SD, standard deviation; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.
^aInformation on LVEF missing in 288 patients.



function, also on the long term. This is in accordance with prior findings from the MOST trial.¹⁵ The programming of a moderately prolonged atrio-ventricular interval in the DDDR pacemakers¹ reducing the mean %VP and allowing atrial emptying may be important for the avoidance of HF. Previous studies indicate that DDD



pacing leads to a poor prognosis in patients with severely compromised left ventricular function.^{7,15} The present study confirms that there is no correlation between %VP and development of HF and, additionally, the ventricular pacing site did not influence HF development. Baseline characteristics, well known to increase risk of HF

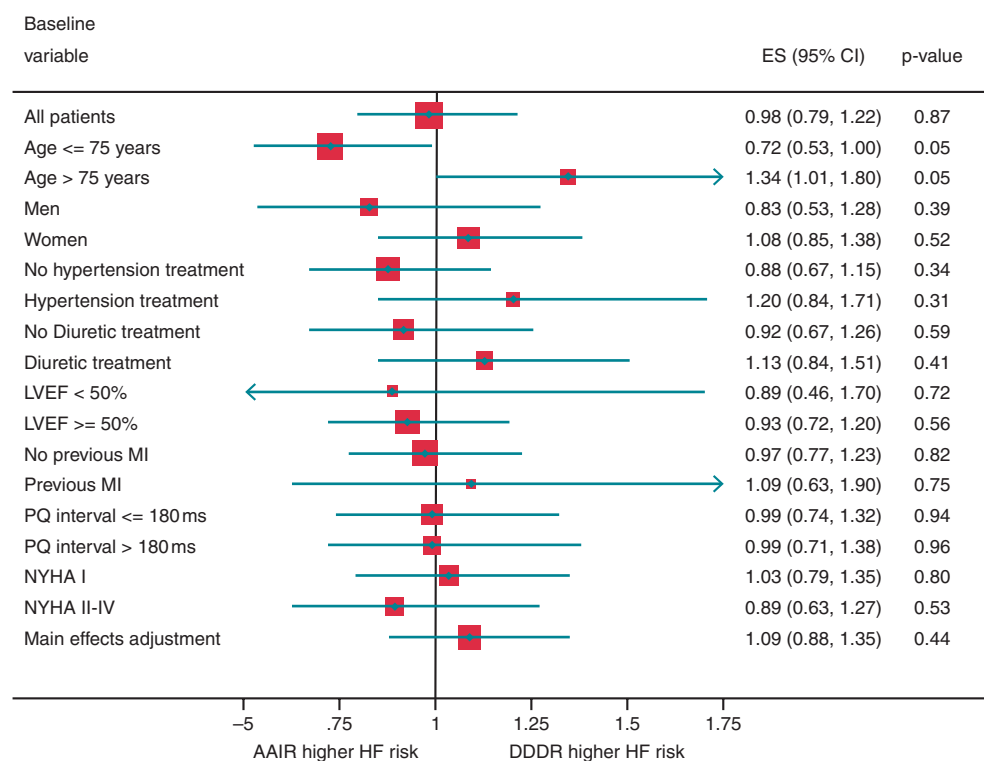


Figure 3 In patients randomized to AAIR or DDDR pacing hazard ratios for development of new heart failure are shown for different sub-groups. Patients were classified with new heart failure, if in New York Heart Association functional class IV or if presence of ≥ 2 of: oedema, dyspnea, and New York Heart Association functional class III. A fully adjusted hazard ratio is displayed at the bottom. CI, confidence interval; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; ES, effect size (hazard ratio).

(age, hypertension, previous MI, reduced systolic function, and increased left ventricular end-diastolic diameter), were found to be associated with both development of clinical HF and HF hospitalizations in our trial.

Lead position

It is well established that right ventricular apical pacing may have acute deleterious effects on left ventricular performance as compared with non-apical lead positions, at least when measured by imaging modalities,^{10,14,16} whereas the right ventricular systolic function may not be affected.¹¹ However, the long-term results of non-apical pacing are ambiguous. Another option is direct His-bundle and para-Hisian pacing which may offer superior electrical and haemodynamic response as compared with apical pacing.^{17–19} Indeed, Occhetta *et al.*¹⁸ showed an improvement in NYHA functional class, 6 min walk test, and quality of life after 6 months of para-Hisian pacing. However, this implantation approach is challenging, requires electrophysiology mapping, and carries a higher risk of lead dislodgement.

Others, however, have not been able to find any acute benefit from pacing from a non-apical vs. an apical position.²⁰ Indeed, documentation for the clinical benefit of non-apical pacing remains scarce, especially among patients with preserved left ventricular function. Most studies are not randomized, include a small number

of patients with relatively short follow-up, and endpoints have been variable and often not directly related to patient outcome.

In the current study, we show that in patients with SSS and preserved AV conduction, treated with DDDR pacemaker, there is no increased risk of HF with right ventricular leads in either the apical or the non-apical positions, although a trend towards better outcome in patients with leads in the non-apical positions was observed. Thus, our study adds to previous publications, which could not demonstrate any convincing clinical benefit from selective site pacing, despite obvious haemodynamic advantages. Three on-going trials randomizing patients to apical or septal pacing (PROTECT PACE, RASP, and OPTIMISE RV) may clarify a possible importance of pacing site.²¹ Still, these trials have left ventricular ejection fraction as the main endpoint and not 'harder' clinical endpoints such as HF, stroke, and death.

Ventricular pacing percentage

From previous studies of the effects of DDDR pacing, it has been the general opinion that the detrimental effects on left ventricular performance were proportionate to the percentage of ventricular pacing (%VP). In the Dual-Chamber and VVI Implantable Defibrillator (DAVID) trial, Wilkoff *et al.*⁷ found that implantable cardioverter-defibrillator patients with severely compromised left ventricular ejection fraction had a poorer outcome with DDDR pacing with a relatively short AVI as compared with VVI back-up

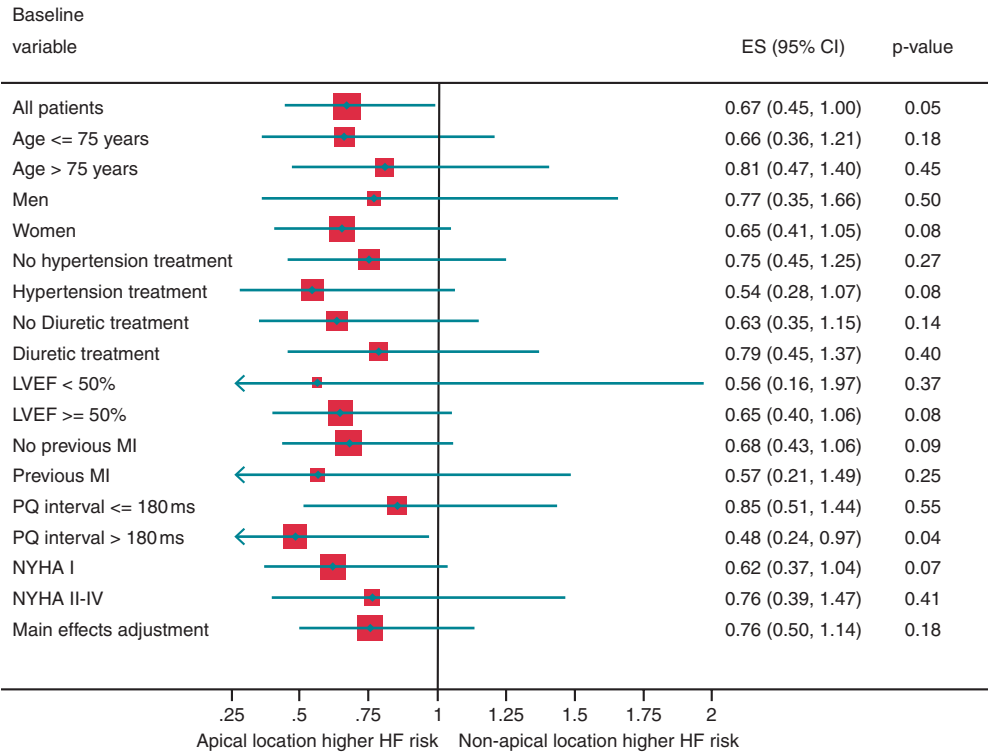


Figure 4 Per protocol analysis in patients with DDDR pacemaker with either apical or non-apical lead positions. Hazard ratios for development of new heart failure are shown for different subgroups. A fully adjusted hazard ratio is displayed at the bottom. CI, confidence interval; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; ES, effect size (hazard ratio).

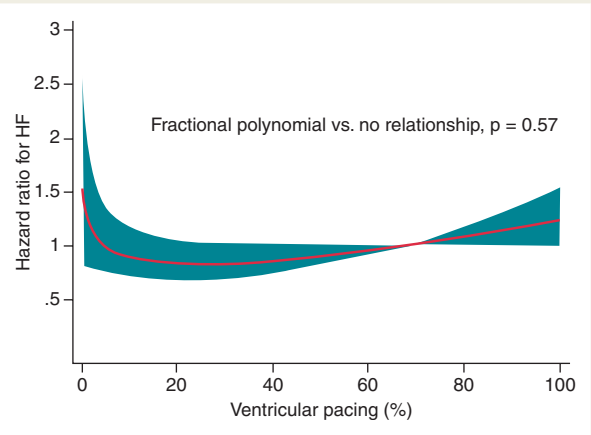


Figure 5 Hazard ratio for the development of heart failure in relation to mean %VP. The median percentage of ventricular pacing in the DDDR group was 85% (interquartile range 34–99%). No significant association was found between %VP and the development of heart failure, fractional polynomial vs. no relationship, $P = 0.57$.

pacing (40 b.p.m.). In the current study, we found no association between %VP and the risk of developing HF. As opposed to the trial by Sweeney et al.,²² DDDR pacemakers in the current study

were programmed with a moderately prolonged AVI (140–220 ms), yet preventing extreme first-degree AV block, which in itself may cause HF symptoms.

Limitations

Echocardiography was only performed at enrolment in the trial. Therefore, diagnosis of HF in the present study rests on symptoms and medication. However, we find it unlikely that our indicators of HF would not identify patients with moderately to severely depressed systolic function.

It is well known that when using only one fluoroscopic view, operators may consider a lead in a septal position, even though it is in fact placed on the anterior free wall of the right ventricle increasing the risk of dyssynchrony and perforation.^{23–25} It was, however, custom in participating centres to review the lead position from the left anterior oblique angle in order to exclude an overly anterior position. We therefore consider it unlikely that a large number of patients have leads positioned in the anterior wall of the right ventricle.

Patients in the present study with ventricular leads were not randomized to an apical or non-apical position of the lead. Neither does the study represent a randomized comparison of the effect of %VP on the development of HF. However, the data were collected prospectively as part of a large randomized multi-centre trial and indicate the incidence of HF, adjusted for %VP, during long-term follow-up.

The initial statistical analysis was performed as a per protocol analysis meaning that some patients transitioned from the randomized AAIR to DDDR pacing modes due to high-grade AV block. However, this number of patients is relatively small and does not offset the results of the analysis.

Conclusion

The present study in a large randomized cohort did not find any difference in development of HF between AAIR and DDDR (with moderately prolonged AVI) pacing modes in patients with SSS. A significant association between HF and right ventricular pacing site (apical vs. non-apical) disappeared with adjustments for baseline variables. Further, the study did not find any association between %VP and development of HF. These findings suggest that DDDR pacing is safe in patients with SSS without increasing the risk of HF.

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Appendix

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IMAGES IN ELECTROPHYSIOLOGY

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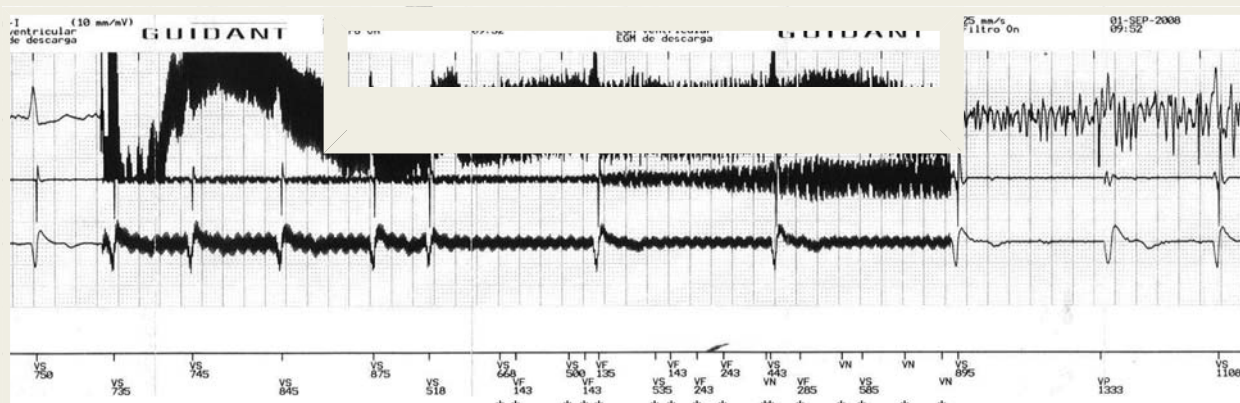
Ventricular oversensing of an implantable cardioverter-defibrillator during electroconvulsive therapy

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Electroconvulsive therapy (ECT) is an effective treatment for severe depressive patients even in high-risk cardiac patients, such as those with an implantable cardioverter-defibrillator (ICD), but current practice guidelines recommend disabling all antitachycardia therapy before each ECT session. We describe a patient with severe psychotic depression who underwent a series of 70 ECT sessions without deactivation of the ICD. The figure shows continuous monitoring of the ICD with the programmer without significant ventricular oversensing. The electrical interference produced minimal noise levels with inappropriate detection of several ventricular



events—asterisks [classified as ventricular sense events, ventricular fibrillation events, and other events classified as noise (VN)]. There were no detections of inappropriate VF episodes and, therefore, there were no inappropriate discharges during the course of 70 ECT sessions. The reported case suggests that even though ICD therapies should be temporarily deactivated, the risk of inappropriate therapy due to ECT seems to be low.

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